REMARKS

I. Status of the Claims

Claims 38-52 are all the claims pending in the application.

Claims 38 and 47 are amended Claim 38 is amended to recite "*Mycobacterium tuberculosis*" and delete the phrase "a hypoxia-responsive element." Claim 47 is amended to a correct minor typographical error.

No new matter is added.

Entry of the Amendment is respectfully requested.

II. Response to Objections to the Claims

Claims 38-52 are objected to because the first instance of the recitation "*M. tuberculosis*" should read "*Mycobacterium tuberculosis*."

Appropriate correction to claim 38 has been made, thereby obviating the objection to claim 38. The objection to claims 39-52 are also obviated, at least by virtue of their dependence from claim 32.

III. Response to Claim Rejections Under 35 U.S.C. § 112

A. Claims 38-52 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Specifically, the recitation of "... the first component being a hypoxia-responsive element..." in claims 38, and the recitation "phosphorylation of the second component" in step (c) in claim 38 is considered new matter by the Examiner.

Initially, claim 38 is amended to delete the recitation of "a hypoxia-responsive element."

Applicants traverse the rejection of step (c) of claim 38.

Claim 38, step (c) is supported by working Example 3 of the present specification, specifically at paragraph [0164], which describes the transphosphorylation from DevS to DevR. Regarding paragraph [0176] of the present specification, the description therein relates to high-throughput assays for screening compound libraries/inhibitors. Therefore, it describes a method wherein the phosphorylation of DevR is inhibited, but only as an analysis tool.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the § 112 rejection of claim 38. The § 112 rejection of claims 39-52 is also overcome, at least by virtue of their dependence from claim 38.

B. Claim 47 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Applicants respectfully submit that in view of the amendment to claim 47 to recite DevS as the first component and DevR as the second component, the § 112 rejection of claim 47 is overcome.

Reconsideration the withdrawal of the rejection are therefore, respectfully requested.

IV. Response to Claim Rejection Under 35 U.S.C. § 103

Claims 38-52 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hoch et al. (U.S. Patent No. 6,043,045) in view of Dasgupta et al. (Tubercular and Lung Disease, 80(3):141-159, 2000) and Sherman et al. (PNAS 98(13):7534-7539, June 19, 2001).

Applicants respectfully traverse the § 103 rejection, at least for the following reasons.

The inventive concept of the present invention lies in correlating the autophosphorylation of DevS or Rv2027C and phosphotransfer to DevR from DevS or Rv2027C. The inventiveness of the present invention is neither in disclosing a two component system nor a high-throughput screening assay for histadine protein kinase for agent identification.

The Examiner has tried to establish a co-relation between inhibition of autophosphorylation and identification of new antibiotics. Further, the Examiner has stated that Dasgupta discloses a two-component system in Mycobacteria and further opined that it is obvious that DevS578, Rv2027194 and DevRN145 would share a common characteristic with DevS, Rv2027C and Dev R because the claimed portion each contain the catalytic site of the molecules, based on the size of transcripts disclosed in the reference. Applicants respectfully disagree.

There are several points of difference between two-component systems although they are classified together on the basis of sequence and functional conservation. Every two-component system is unique in its functional activity and regulation which cannot be predicted merely by examination of the protein sequence in silico. In other words, knowing the properties of KinA Spo0F do not provide any understanding of the DevS/Rv2027c-DevR system. Some of the differences are as follows:

1. System composition and organization

The KinA-Spo0F system described by the Hoch patent, constitutes a phosphorelay along with KinB, Spo0B and Spo0A (the final recipient of the phosphor signal and the regulator of the sporulation pathway). In contrast, DevS/Rv2027c directly transfer the phosphosignal to DevR. Thus DevS/Rv2027c-DevR is a typical two component His-Asp system whereas KinA system is a multicomponent His-Asp-His-Asp phosphorelay in which all the signaling domains are independent proteins. See Stock et al. (2000) Annual. Rev. Biochem. 69:183-215.

In another example, the ResE-ResD system of *B. subtilis*, phosphosignal is directly transferred from ResE to ResD unlike the KinA Spo0A system but like the DevS/Rv2027c-DevR system. See Nakano et al. (2001) J. Bacteriol. 183:1938-1944.

2. Regulatory mechanisms:

Different systems employ different mechanisms to regulate their activity. See Stock, et al. There are examples of histidine kinase activity regulation (both kinase and phosphatase activities) and also response regulator dephosphorylation regulation.

a. For example, in the KinA Spo0F system, kinase activity resides in KinA while phosphatase activity resides in separate proteins (RapA, RapB and RapE) that dephosphorylate Spo0F. In the DevS/Rv2027c –DevR system, the phosphatase activity appears to reside in DevS/Rv2027c kinase. In the ResE-ResD system of B. subtilis, phosphatase activity is present in ResE (in the kinase protein itself). See Nakano, et al.

b. Stability of phosphorylated response regulators varies significantly between various systems (half-lives ranging from seconds to hours and days). For example, CheY~P has a half-life of 0.5 min, NarL of 30 min, Spo0F of 180 min and VanR 540 min. See Zapf et al. (1998) Biochemistry 37:7725-7732.

Thus it is evident that every two-component system is unique in its functional activity and regulation which cannot be predicted merely by examination of the protein sequence in silico. In other words, knowing the properties of KinA Spo0F do not provide us with any understanding of the DevS/Rv2027c-DevR system.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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